Class Discussion:

Haseman, J.K. and R.C. Elston, 1972, "The investigation of linkage between a quantitative trait and a marker locus", Behavior Genetics, Vol. 2, No. 1, 3-19.

1 An Overview

Haseman and Elston (1972) paper on quantitative traits was among the substantial developments in the 1970s. As of today there are many extensions of the method; it is thus worthy to review it for some fundamental insight what the present methodologies work. From these understanding we conceive that indeed the recent plethora about sib-pair analysis does not happen overnight.

Here I would highlight some points of its formulation and its practical applications. That paper dealt with QTL, however, the topic itself does not restrict us to quantitative trait only.

2 The main material

2.1 The problem

It's not a easy matter in man to establish a trait with a genetic component. Different existing methods all have their drawbacks. Here are the points made in the paper.

- Twin studies tends to overestimate the genetic component (H-E 1970).
- Classical segregation analysis only apply to qualitative trait.
- Linkage analysis of trait and marker would be very helpful, especially when increasing number of marker loci available in man. The focus on sib pairs avoid secular or age effects. Penrose first considered the sib pair data, but this paper allowed for incorporation of parental information on marker loci. The recombination fraction was also addressed.

While parametric linkage analysis depends heavily on the model specifications (e.g., the penetrance) and has difficulty in collecting large pedigrees,

sib-pair analysis requires no such assumptions and thus more robust and easy to implement in terms of its design and computation. The drawback might be a larger sample size is necessary. In general it is a very powerful strategy comparable to association analysis, TDT and parametric linkage analysis.

2.2 Some terms

- IBD/IBS. Any two copies of allele 1 at a given locus are considered to be identical by state (IBS), but only copies from allele 1 that are inherited from a common ancestral source are said to be identical by descent(IBD). If two alleles are IBD, they are also IBS.

- Linkage equilibrium. It refers to the situation where genes segregate independently. If linkage disequilibrium occurs we also term it as allelic association.

- Genetic heterogeneity. Any of a number of genetic causes can act independently to produce an identical disease phenotype.

- Phenocopy. The phenotype is simply a copy from environment. In model specification this means we have non-zero penetrances for all genotypes.

2.3 The genetic model

The model is

$$x = \mu + g + e$$

where μ is the overall mean, g is a major gene effect, and e is an environmental effect independent of g. g is a, d and $-a$ for unobserved genotype BB, Bb and bb. $E(g) = E(e) = 0$.

To apply the above equation to sib pair we have $x_{1j} = \mu + g_{1j} + e_{1j}$, $x_{2j} = g_{2j} + e_{2j}$ From these we could expect a relation for the squared pair difference $Y_j = (x_{1j} - x_{2j})^2$ of sib pair j, under any possible combinations as listed in H-E table I.

- $\pi_j = 0$ signifies sibs are "unrelated" at the trait locus, so the distribution simply follows the usual Hardy-Weinberg Law of random-mating population.

Table 1: Conditional Distribution of Y_j

		Conditional probability		
Sib pair	Y_j	$\pi_j = 0$	$\pi_j = \frac{1}{2}$	$\pi_j = 1$
BB-BB	e_j^2	p^4	p^3	p^2
bb-bb	e_j^2	q^4	q^3	q^2
Bb-Bb	e_j^2	$4p^2q^2$	pq	$2pq$
BB-Bb	$(a - d + e_j)^2$	$2p^3q$	p^2q	0
Bb-BB	$(-a + d + e_j)^2$	$2p^3q$	p^2q	0
Bb-bb	$(d + d + e_j)^2$	$2pq^3$	pq^2	0
bb-Bb	$(-a - d + e_j)^2$	$2pq^3$	pq^2	0
BB-bb	$(2a + e_j)^2$	p^2q^2	0	0
bb-BB	$(-2a + e_j)^2$	p^2q^2	0	0

- $\pi_j = 1$ when both sibs have the same genotype so the probability is just the probability in population of one of them.
- $\pi_j = \frac{1}{2}$ is similarly reasoned yet more complicated.

From table 1, we can have the expected value of Y_j given $\pi_j, j = 0, \frac{1}{2}, 1$, i.e.,

$$E[Y_j|\pi_j] = \sigma_e^2 + 2\sigma_a^2 + 2\sigma_d^2, \quad \sigma_e^2 + \sigma_a^2 + 2\sigma_d^2, \quad \sigma_e^2$$

and in a more general case

$$E[Y_j|\pi_j] = (\sigma_e^2 + 2\sigma_g^2) - \pi_j[2\sigma_g^2 + 2n_1(n_2 - n_0)\sigma_d^2/(4n_0n_2 + n_0n_1 + n_1n_2)]$$

Assuming no dominance ($d = 0$ or $\sigma_d = 0$) we see that $E(Y_j|\pi_j) = \alpha + \beta\pi_j, \alpha = {\sigma_e}^2 + 2{\sigma_g}^2$, and $\beta = -2{\sigma_g}^2$.

In a more general formulation, a term for polygenic effect and/or covariates may also be included. It is familiar to see this for variance components/path analysis models.

In derivation of the variance of a quantitative trait, we take BB, Bb and bb as $2\alpha, \alpha, 0$ respectively, by considering that the variance is independent of origin. Thus in a random-mating population, the mean and variance (genetic variance of the population) would be $2p\alpha$ and $2pq\alpha^2$. In many situations it is convenient to take genic effect as unit of measurement, then g has values 2, 1, 0 and the mean and variance change to $2p$ and $2pq$.

To determine the effect of dominance on the variance, we fit a set of hypothetical G values for which the effect of each gene substitution is constant. The phenotypic and fitted values then have relationship ${\sigma_x}^2 = {\sigma_a}^2 + {\sigma_d}^2$ The fit of $X = G + D$, D has forms D_{BB}, D_{Bb} and D_{bb}, is by minimizing

$$\Delta = \Sigma f D^2 = p^2 {D_{bb}}^2 + 2pq {D_{Bb}}^2 + q^2 {D_{bb}}^2$$

then

$$D_{BB} = -q^2(h_1 - h_2)$$
$$D_{Bb} = pq(h_1 - h_2)$$
$$D_{bb} = -p^2(h_1 - h_2)$$

where $h_1 = x_{Bb} - x_{bb}, h_2 = x_{BB} - x_{Bb}$ and α could be obtained see, Li(1955).

$${\sigma_a}^2 = 2pq\alpha^2 = 2pq(ph_2 + qh_1)^2, {\sigma_D}^2 = p^2q^2(h_1 - h_2)^2$$

We have

$${\sigma_a}^2 = 2pq[a - d(p - q)]^2 \quad {\sigma_d}^2 = 4p^2q^2d^2$$

2.4 Including marker information

Let f_{ji} be the probability that j^{th} sib pair has i alleles IBD at the marker locus, $i = 0, 1, 2$ conditional on the nuclear family data available, then π_j, the proportion of alleles the j^{th} sib pair shares IBD at the marker locus, is given by $\hat{\pi}_j = f_{j2} + \frac{1}{2} f_{j1}$. The proportion of alleles the j^{th} half-sib pair share IBD at the marker locus is estimated by $\hat{\pi}_j = \frac{1}{2} f_{j1}$.

With half-sibs, one schematic form is as follows.

$$\boxed{1} \quad \underset{\downarrow}{\rightarrow\leftarrow} \quad (2) \quad \underset{\downarrow}{\rightarrow\leftarrow} \quad \boxed{3}$$
$$\boxed{S_1} \qquad \boxed{S_2}$$

It would display a 'cluster' format (SAGE/SIBPAL) if any parent has more than three spouses and then another kinds of sibs.

The same reasoning process applies to the estimation involving marker information, i.e., the notion of mating type and conditional probability, as shown in E-H table II.

Table 2: $\hat{\pi}_j$ when both parental and sib genotypes are known

Mating type		Sib pair type		Probability	f_{j0}	f_{j1}	f_{j2}	$\hat{\pi}_j$
I:	$A_iA_i \times A_iA_i$	I:	$A_iA_i - A_iA_i$	p_i^4	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{2}$
II:	$A_iA_i \times A_jA_j$	V:	$A_iA_j - A_iA_j$	$2p_i^2p_j^2$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{2}$
III:	$A_iA_i \times A_iA_j$	I:	$A_iA_i - A_iA_i$	$p_i^3p_j$	0	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{3}{4}$
		III:	$A_iA_i - A_iA_j$	$2p_i^3p_j$	$\frac{1}{2}$	$\frac{1}{2}$	0	$\frac{1}{4}$
		V:	$A_iA_j - A_iA_j$	$p_i^3p_j$	0	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{3}{4}$
IV:	$A_iA_i \times A_jA_k$	V:	(2)	$p_i^2p_jp_k$	0	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{3}{4}$
		VI:	$A_iA_j \times A_iA_k$	$2p_i^2p_jp_k$	$\frac{1}{2}$	$\frac{1}{2}$	0	$\frac{1}{4}$
V:	$A_iA_j \times A_iA_j$	I:	(2)	$p_i^2p_j^2/4$	0	0	1	1
		II:	$A_iA_i \times A_jA_j$	$p_i^2p_j^2/2$	1	0	0	0
		III:	(2)	$p_i^2p_j^2$	0	1	0	$\frac{1}{2}$
		V:	$A_iA_j \times A_iA_j$	$p_i^2p_j^2$	$\frac{1}{2}$	0	$\frac{1}{2}$	$\frac{1}{2}$
VI:	$A_iA_j \times A_iA_k$	I:	$A_iA_i - A_iA_i$	$p_i^2p_jp_k/2$	0	0	1	1
		III:	(2)	$p_i^2p_ip_k$	0	1	0	$\frac{1}{2}$
		IV:	$A_iA_i - A_jA_k$	$p_i^2p_jp_k$	1	0	0	0
		V:	(3)	$p_i^2p_jp_k/2$	0	0	1	1
		VI:	$A_iA_j - A_iA_k$	$p_i^2p_jp_k$	1	0	0	0
		VI:	$\begin{smallmatrix}A_iA_j-A_jA_k\\A_iA_k-A_jA_k\end{smallmatrix}$	$p_i^2p_jp_k$	0	1	0	$\frac{1}{2}$
VII:	$A_iA_i \times A_kA_l$	V:	(4)	$p_ip_jp_kp_l/2$	0	0	1	1
		VI:	(4)	$p_ip_jp_kp_l$	0	1	0	$\frac{1}{2}$
		VII:	(2)	$p_ip_jp_kp_l$	1	0	0	0

With any genotypic information unknown, f_{ji} would be more difficult to obtain, an estimation needs to be done from the parent and offspring phenosets.

$$f_{ji} = \frac{\sum_{\nu \in P_P} \sum_{w \in P_S} P(\nu \texttt{ and } w \texttt{ and } \pi_j = \frac{i}{2})}{\sum_{h=0}^{2} \sum_{\nu \in P_P} \sum_{w \in P_S} P(v \texttt{ and } w \texttt{ and } \pi_j = \frac{h}{2})}$$

where $i = 0, 1, 2$.

The numerator is the joint probability of observing I_m and that π_j equals $\frac{i}{2}$; the denominator is the sum of the three such joint probability for $i = 0, 1, 2$. Results for no dominance and no parental information is given in their table III (here $\Phi = (1 + p_i + p_j + 2p_ip_j)$).

Table 3: $\hat{\pi}_j$ when there is no dominance and parental genotypes are unknown

Sib pair type		Probability	f_{j0}	f_{j1}	f_{j2}	$\hat{\pi}_j$
I:	$A_iA_i \times A_iA_i$	$p_i^2(1+p_i)^2/4$	$\frac{p_i^2}{(1+p_i)^2}$	$\frac{2p_i}{(1+p_i)^2}$	$\frac{1}{(1+p_i)^2}$	$\frac{1}{(1+p_i)}$
II:	$A_iA_i \times A_jA_j$	$p_i^2p_j^2/2$	1	0	0	0
III:	$A_iA_i \times A_iA_j$	$p_i^2p_j(1+p_i)$	$\frac{p_i}{1+p_i}$	$\frac{1}{1+p_i}$	0	$\frac{1}{2(1+p_i)}$
IV:	$A_iA_i \times A_jA_k$	$p_i^2p_jp_k$	1	0	0	0
V:	$A_iA_j \times A_iA_j$	$p_ip_j\Phi/2$	$\frac{2p_ip_j}{\Phi}$	$\frac{p_i+p_j}{\Phi}$	$\frac{1}{\Phi}$	$\frac{2+p_i+p_j}{2\Phi}$
VI:	$A_iA_j \times A_iA_k$	$p_ip_jp_k(1+2p_i)$	$\frac{2p_i}{1+2p_2}$	$\frac{1}{1+2p_i}$	0	$\frac{1}{2(1+2p_i)}$
VII:	$A_iA_j \times A_kA_l$	$2p_ip_jp_kp_l$	1	0	0	0

2.5 Other aspects

The null hypothesis for usual linkage analysis is $H_0 : c = 0; H_1 = \frac{1}{2}$. It turns out simple to bear that the test is $H_0 : slope = 0$ vs $H_1 : slope < 0$ where linkage is expected.

$$\begin{aligned} E[Y_j|\hat{\pi}_{jm}] &= \sum_{\pi_{jk}} E(Y_j|\pi_{jt})P(\pi_{jt}|\hat{\pi}_{jm}) \\ &= \sum_{\pi_{jt}}\sum_{\pi_{jm}} E(Y_j|\pi_{jt})P(\pi_{jt}|\pi_{jm})P(\pi_{jm}|\hat{\pi}_{jm}) \end{aligned}$$

The first part simply combines all the possibilities given marker data while the second part relates to a clever inclusion of marker probability.

Table 4: Joint distribution of π_{jm} and π_{jt}

	π_{jm}			
π_{jt}	0	$\frac{1}{2}$	1	Total
0	$\Psi^2/4$	$\Psi(1-\Psi)/2$	$(1-\Psi)^2/4$	$\frac{1}{4}$
$\frac{1}{2}$	$\Psi(1-\Psi)/2$	$(1-2\Psi+2\Psi^2)/2$	$\Psi(1-\Psi)/2$	$\frac{1}{2}$
1	$(1-\Psi)^2/4$	$\Psi(1-\Psi)/2$	$\Psi^2/4$	$\frac{1}{4}$
Total	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$	1

It deserves to note the way recombination fraction c was included in the model described in their appendix B. The joint distribution of π_{jm} and $\hat{\pi}_{jm}$ can be derived from table II. For the special case of a two-allele marker gene this was given in table V.

Table 5: Joint distribution of $\hat{\pi}_{jm}$ and π_{jt} for a two-allele marker locus with no dominance and complete parental information

	π_{jm}			
$\hat{\pi}_{jm}$	0	$\frac{1}{2}$	1	Total
0	$\frac{1}{2}p^2q^2$	0	0	$\frac{1}{2}p^2q^2$
$\frac{1}{4}$	p^3q+pq^3	p^3q+pq^3	0	$2(p^3q+pq^3)$
$\frac{1}{2}$	$\frac{1}{4}(p^4+4p^2q^2+q^4)$	$\frac{1}{2}(p^4+6p^2q^2+q^4)$	$\frac{1}{4}(p^4+4p^2q^2+q^4)$	$(p^4+5p^2q^2+q^4)$
$\frac{3}{4}$	0	p^3q+pq^3	p^3q+pq^3	$2(p^3q+pq^3)$
1	0	0	$\frac{1}{2}p^2q^2$	$\frac{1}{2}p^2q^2$
Total	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$	1

Note the conditional probabilities of $p(\pi_{jt}|\pi_{jm})$ and $p(\pi_{jm}|\hat{\pi}_{jm})$: the first elements of $p(\pi_{jt}|\pi_{jm})$ is

$\frac{\Psi^2/4}{1/4}, \frac{\Psi(1-\Psi)/2}{1/2}, \frac{(1-\Psi)^2/4}{1/4}$ and the other two elements are obtained accordingly, here $\Psi = c^2 + (1-c)^2$. Formulation of $p(\pi_{jm}|\hat{\pi}_{jm})$ is similar.

For $E[Y_{jt}|\hat{\pi}_{jm} = 1]$, it is

$$\sigma_e^2\Psi^2 + [\sigma_e^2 + \sigma_g^2][2\Psi(1-\Psi)] + [\sigma_e^2 + 2\sigma_g^2][(1-\Psi)^2]$$

that equals to ${\sigma_e}^2 + 2(1-\Psi){\sigma_g}^2$. The derivation of $E(Y_{jt}|\hat{\pi} = \frac{1}{2})$ is a bit tedious.

In summary, the expression for $E[Y_{jt}|\hat{\pi}_{jm}]$ is

$$[{\sigma_e}^2 + 2(1-2c+2c^2){\sigma_g}^2] - 2(1-2c)^2{\sigma_g}^2\hat{\pi}_{jm}$$

This simply has the form

$$E[Y_j|\hat{\pi}_j] = \alpha + \beta\hat{\pi}_j$$

where $\beta = -2(1-2c)^2{\sigma_g}^2$.

The test of the null hypothesis of no linkage turns out to be a test of β a significantly non-zero of β implies linkage, i.e., $c \neq \frac{1}{2}$

Further, suppose that there are K trait loci, each linked to the trait loci, c be recombination fraction, they shows

$$E[\hat{\beta}] = -2\sum_{i=1}^{K}(1-2c_i)^2{\sigma_i}^2$$

where ${\sigma_i}^2$ is the component of total genetic variance of the i^{th} trait locus.

The underlying assumption would be K trait loci are mutually unlinked and there is no epistasis.

2.6 Maximum likelihood estimation of linkage

The proposed method has a disadvantage that σ_g^2 is confounded with recombination fraction c so that linkage could only be detected but not estimated. The paper proceeds to assume sib pair differences are normally distributed as a mixture of up to seven normal distributions. By considering only the absolution pair differences the number of distributions could be reduced to four f_1,f_2,f_3,f_4. They showed that the likelihood function for a sib pair can be expressed as in terms of five parameters c, p, σ_e^2, and d,

$$L = f(D|I_m) = \sum_{h=0}^{2}\sum_{k=0}^{2} f(D_j|\pi_{jt} = h/2)P(\pi_{jt} = h/2|\pi_{jm} = k/2)P(\pi_{jm} = k/2|I_m)$$

where $f(D_j|\pi_{jt} = h/2) = m_{h1}f_1 + m_{h2}f_2 + m_{h3}f_3 + m_{h4}f_4$. Values of m_{hi}, $h = 0, 1, 2$; $i = 1, 2, 3, 4$ can be obtained from table I and were given in table VI.

Table 6: Values of the coefficient m_{hi}

	1	2	3	4
0	$p^4 + 4p^2q^2 + q^4$	$4p^3q$	$4pq^3$	$2p^2q^2$
1	$1 - 2pq$	$2p^2q$	$2pq^2$	0
2	1	0	0	0

3 Extensions

Like many other commonly used linkage procedures, it assumes linkage equilibrium and no clinical and genetic heterogeneity.

In addition to notes above, one conceivable example is that we need to take the effect of sibship size into considerations, as proposed by Hodge (1984) and implemented in GAS (Genetic Analysis System).

Blackwelder and Elston (1985) and later Knapp et al (1994) described the power of various statistics of affected sib pair analysis; Goldgar(1990) handles

multipoint human data on multifactorial traits but confounds the effect of the linked quantitative trait loci with the total additive genetic variance. H-E method was extended by Amos and Elston (1989) to other types of relative pairs. Amos(1994) discussed the estimation of the recombination fraction from relative pair data using likelihood and quasi-likelihood methods.

For highly polymorphic marker such as HLA, IBS information is also invaluable, see Lange (1986). For diseases with a late age of onset, many parental couples will be unavailable for genic typing. The method classifies affected sib pairs based on IBS information as concordant, discordant and half-maker concordant without referring to parental genotypes. It's possible to compare the expected and observed number of affected sib-pairs falling into each categories by χ^2 test. The method was also extended to consider multiple sibs.

Sib-pair interval mapping is a multi-point method in which information from adjacent markers is used to infer missing or ambiguous allele sharing.

$$x_i = \mu + g_i + G_i + \sum_{k=1}^{s} \beta_k z_{ik} + e_i$$

z_{ik} is the kth covariate measurement on an individual. $g_i = a, d, -a$ for BB, Bb and bb, $E(g_i) = E(e_i) = E(G_i) = 0$. G_i is a random polygenic effect. We have $E(x_i) = \mu + \sum_{k=1}^{s} \beta_k z_{ik}$ and $COV(x_i, x_j) = {\sigma_a}^2 + {\sigma_d}^2 + {\sigma_G}^2 + {\sigma_e}^2$ for i=j and $\Phi_{ij}{\sigma_a}^2 + \Delta_{ij}\sigma_d^2 + \Phi_{ij}\sigma_G^2$ for $i \neq j$, where σ_g^2 and σ_e^2 are respectively, the polygenic and residual components of variance. and σ_a^2 and σ_d^2 as before. Φ_{ij} is the coefficient of relationship between relatives, Δ_{ij} is the probability a pair shares both alleles at the major locus IBD. With marker data available $E(x_i|\pi_{tij})$ and $COV(x_i, x_j|\pi_{tij})$ have similar expressions. With linked markers, $E(x_i - x_j|\pi_{ij}) = 2Var(x_i^2) - 2cov(x_i x_j|\pi_{ij})$, now $cov(x_i, x_j|\pi_{ij})$ includes marker information. When joint distribution of is multinormal, then we have likelihood function to which optimization or other estimation methods can be applied, see Amos (1994).

Affected sib-pair analysis (ASP) is more widely used in the linkage design and analysis. It avoids incomplete penetrance and supposes that if a given marker is cosegregating with a disease- predisposing allele, then affected siblings of affected persons are more likely to receive the same allele identical by descent at a closely linked marker locus than if the marker locus was segregating independently.

The Extended Sib pair analysis (ESPA) calculates a chi-square test statistic $\chi^2 = 2[S - E(S)]^2/E(S), E(S) = [S + NS]/2$, S and NS are number of observed allele shared/not shared IBD, of the null hypothesis of no linkage. It employs LINKAGE/MLINK program to estimate the possible marker genotypes for untyped individuals. Thus IBD is a probability count that may lead to bias.

In extended pedigree to examine IBS relationships, the so-called affected pedigree member (APM) method. The statistic is

$Z_{ij} = \frac{1}{4}\sum_{a=1}^{2}\sum_{b=1}^{a}\delta(A_a, B_b)f(A_a)$, where $f(A_a)$ is a weight function taking forms of $1, 1/\sqrt{p_{A_a}}, 1/\sqrt{p_{A_a}}$, the latter two give more weight to rare-allele sharing.

Other scheme may include study design, see for instance, Boehnke (1990) and Risch and Zhang (1995). Actually these papers considered the quantitative traits in their extremity values. To avoid the influence of allele frequencies, affected sib-pair with parental information is attractive.

4 Implementations

Some aspects that have been considered:

- Information contained in multiple sibs
- Complex sibship and pedigree structure
- Estimation of possible genotype
- Multiloci or haplotype, its implementation
- Covariates

Here are a few softwares that are useful.

- SAGE/SIBPAL could handle both qualitative and binary trait with or without variable age of onset. It can also take covariates.
- ESPA is used for 'extended' sib-pair analysis.

- GAS/SIBHE GAS 2.0 has graphic utility for PostScript file. Among others, GAS/SIBIHE combines interval mapping with the H-E algorithm. It also uses Jeff O'Connell's Vitesse program. It is able to handle up to 8 highly polymorphic loci simultaneously. It also has modules for IBD and Lange's IBS analysis referred above.

- APM may ignore information on relative haplotype and also depends heavily on allele frequencies.

User control. GAS, MAPMAKER/SIBS provide user-friendly commands. However most programs use LINKAGE/MAKEPED .PED format or .PRE.

5 Applications

The method has wide application, such as serum IgE level with interleukin-4 encoding gene, the angiotensinogen(IBS-APM) and essential hypertension, Alzheimer's Disease(late-onset with chromosome 19). Actually the basic theory has become one of the strategies for genetic dissection of complex trait. Affected sib-pair have played an important role in the study of type I diabetes and HLA.

Acknowledgements

In writing this, some of the descriptions are excerpts from the original papers due to time limitations; some changes are made to consist with H-E's original paper.

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